PhRMA

July 23, 1998

Dockets Management Branch (HFA-305)
Food and Drug Administration
12420 Parklawn Drive, room 1-23
Rockville, MD 20857

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Re: PhRMA Comments on FDA's Proposed Rule on the Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices, 63 Fed. Reg. 31143 (June 8, 1997) Docket No. 98N-0222

Dear Sir/Madam:

Enclosed for submission to the above-referenced docket are comments by the Pharmaceutical Research and Manufacturers of America (PhRMA) regarding FDA's June 8 proposed rule implementing section 401 of the FDA Modernization Act of 1997 (FDAMA) on the dissemination of new treatment information. PhRMA represents America's leading research-based pharmaceutical and biotechnology companies; in 1998, P W members will devote almost 20 percent of overall sales to research and development – more than $20 billion. PhRMA companies are leading the way in the search for cures, and are committed to providing the health care community scientifically sound treatment information of the type covered by section 401. The enclosed comments address the proper implementation of section401, and amplify and expand upon P hRMA remarks presented at a July 8, 1998 public meeting held by FDA regarding the June 8 Dissemination proposal.

Section 401 represents a significant change from FDA's traditional prohibition on the dissemination of any off-label information. This provision, which arose out of a bipartisan agreement, is intended by Congress to balance two objectives: (1) to facilitate the sharing of important treatment information with health care providers to enable better patient care in accordance with current medical knowledge, and (2) to ensure that research leading to new labeled uses continues to be undertaken.

Unfortunately, as detailed in the enclosed comments, FDA's proposal not only fails to achieve this balance, but actually threatens the real-world utility of section 401. The proposal evidently seeks to treat the dissemination of peer-reviewed journal articles to health care providers as ordinary promotion – which it is not. Most importantly, by expanding the nature and scope of required administrative review and narrowing the criteria for qualifying peer-reviewed journal articles and reference texts, the proposal threatens to prevent or severely deter the dissemination of the core materials that Congress specifically meant to facilitate in enacting section401.

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In addition to the enclosed comments, and the July 8 testimony, PhRMA on May 29 submitted a recommended approach for implementing section401. These and other FDAMA submissions are available on our website (www.phrma.org). PhRMA welcomes these opportunities to provide input on this important FDAMA provision, and remains available to participate with additional comments and other input during FDA's public process for implementing FDAMA.

Sincerely yours,

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Schering-Plough Corporation
Chair, PhRMA Dissemination Work Group
908/298-5770 (908/740-5770 after August 15)

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Enclosure

P hRMA Comments on FDA's June 8, 1998, Dissemination Proposal

cc: Margaret M. Dotzel, Office of Policy, FDA
Jane Axelrad and Laurie Burke, CDER/FDA
Toni Stifano, CBER/FDA

July 23, 1998

COMMENTS OF THE PHARMACEUTICAL RESEARCH
AND MANUFACTURERS OF AMERICA

ON

FDA's PROPOSED RULE ON THE DISSEMINATION OF INFORMATION ON
UNAPPROVED/NEW USES FOR MARKETED DRUGS, BIOLOGICS, AND DEVICES
63 Fed. Reg. 31143 (June 8, 1998)

DOCKET NO. 98N-0222

SUBMITTED TO THE DOCKETS MANAGEMENT BRANCH
OF THE FOOD AND DRUG ADMINISTRATION

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies. PhRMA companies are devoted to inventing medicines that allow patients to lead longer, happier, healthier and more productive lives. Investing over $20 billion a year in discovering and developing new treatments, PhRMA companies are leading the way in the search for cures.

As pioneers in the discovery and development of new treatments, PhRMA companies are committed to providing medical information to health care providers to enable better patient care in accordance with current medical and scientific knowledge. Section401 of the Food and Drug Administration Modernization Act of 19971 creates an important new mechanism for disseminating information to health care professionals on the safety, effectiveness, and benefits of new uses of approved drugs. As Congress explained when enacting Section401, " [t]he principal policy considerations that underlie this provision are the facilitation of greater access to

[1] Pub. L. No. 105-115, 111 Stat. 2296,2356-65 (Nov. 21, 1997) (codified in the Federal Food, Drug and Cosmetic Act as a new Subchapter D, "Dissemination of Information on New Uses," §§ 551-557; 21 U.S.C. §§ 360aaa to 360aaa-6).

timely and accurate information by health care providers." H.R. Rep. No. 105-310 at 60 (1997). Companies could not previously disseminate medical or scientific information on new/unapproved uses, unless they were responding to unsolicited requests for such information from physicians; however, as William Schultz, FDA's Deputy Commissioner for Policy, stated at the July 8, 1998 public hearing FDA held on Section 401, Congress enacted Section 401 to "change the rules."

In changing the rules, Congress established very detailed requirements for the dissemination of treatment information on new/unapproved indications in order to ensure the scientific soundness and balance of disseminated information and encourage the eventual inclusion of such information in product labeling. These detailed requirements that Congress has already established by statute delineate what type of information on unapproved/new uses may be disseminated, in what manner, under what circumstances, to whom. Although some aspects of the statutory scheme can and should be clarified by implementing regulations, FDA's proposed rule[2] goes much further and imposes significant new requirements and constraints to narrow Section 401 in contravention of both the letter and intent of the statute.

FDA appears to be treating dissemination as if it were ordinary promotion. Indeed, one of the notices FDA published announcing the July 8, 1998 public meeting on Section401 stated that the meeting would discuss "off-label use promotion." The head of FDA's Office of Consumer Affairs repeated that characterization at the start of the July 8 public meeting. However, the dissemination of unabridged medical and scientific information from reputable journals and reference publications is distinct from promotion, as Congress recognized.

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[2] 63 Fed. Reg. 31143 (June 8, 1998).

An understanding of certain basic premises underlying Section 401 is crucial to implementing the statute in a manner that is faithful to Congress's intent. First, the primary safeguard in the statutory scheme for ensuring the scientific soundness and validity of the information is the threshold requirement that a reprint or reference text will have been reviewed by independent experts. Under Section 401, reprints of articles may only be disseminated if they were published by scientific or medical journals that have an editorial board, utilize independent experts to review and select articles, impose financial disclosure rules on authors and contributors, have established peer review procedures, are generally recognized to be of "national scope and reputation," are indexed in the Index Medicus of the National Library of Medicine of the National Institutes of Health, and are not funded by manufacturers. Federal Food, Drug, and Cosmetic Act (FFDCA) § 556(5); 21 U.S.C. § 360aaa-5(5). Reference publications must be prepared independently of the manufacturer, not be edited or significantly influenced by the manufacturer, and be generally available in bookstores or other distribution channels where medical textbooks are sold. FFDCA § 552(b); 21 U. S.C. § 360aaa- 1 (b). Previous] y companies could provide these types of materials only reactively upon the unsolicited request of a physician; as an additional measure, Congress enacted 401 to allow companies to provide the information proactively. Whatever the specific regulatory guidelines and procedures that FDA establishes, they cannot at the end of the day preclude or significantly deter the dissemination of the reprints or reference textbooks that Congress clearly intended to be disseminated.

Second, Congress intended FDA's review of materials on new/unapproved uses, although a central component of Section401, to be limited in scope. For example, Congress explained that although FDA will review the balance of a proposed dissemination, Congress "does not intend this to be an opportunity for [FDA] to editorialize based on independently derived

scientific information. " H.R. Rep. No. 105-310 at 60. FDA will be able to conduct a full clinical review of the safety and efficacy of the new use at a later time, because companies must file a supplement for the new use, unless doing so would be economically prohibitive or require conducting what would be unethical clinical studies. See FFDCA § 554; 21 U.S.C. § 360aaa-3. Section 401 essentially sets Up a notice and review process, to be followed by an ongoing dialogue between the FDA and a company regarding the filing and review of a supplement. The review portion of the procedure at the preliminary stage applicable to the reprint or reference publication only involves FDA's determination that the proposed dissemination package is objective and balanced, is not false or misleading, and contains the disclaimers and certifications required by Section401.

In imposing what appear to be new and additional requirements to expand the nature and scope of its review and narrow the criteria for qualifying articles and texts, FDA's proposed rule threatens to prevent or severely deter the dissemination of the core materials that Congress specifically envisioned in enacting Section 401, rather than facilitating their dissemination. The particular provisions of FDA's proposed rule which must be revised or clarified to avoid such an unfortunate and unacceptable result are discussed below.

1. Definition of "New Use" [Proposed § 99.3(g)]

Nothing that FDA does in the course of implementing Section 401 can or should reduce the sphere of authorized promotional or other practices that preexisted Section401. Congress enacted Section 401 against the backdrop of those preexisting standards, and passed Section401 only to allow the proactive dissemination of qualifying j ournal articles and reference publications. To the extent any FDA action could be read to cast doubt on any practices permitted outside of the scope of Section 401, they would be completely improper. FDA's

proposed definition of "new use" properly mirrors the statutory definition. *Compare* Proposed § 99.3(g) *with* FFDCA § *556(4);* 21 U.S.C. § 360aaa-5(4). However, in the preamble to its proposed regulations, FDA discusses "new uses" in an inaccurate and expansive manner that could be interpreted improperly to suggest that FDA might seek to apply the new regulations to the distribution of information on certain *approved* uses. In that preamble, FDA states that

> "New uses" that would require approval of a supplemental application to add the use to the labeling of an approved drug . . . and that, therefore, would be covered by this part include, but are not limited to: a completely different indication; modification of an existing indication to include a new dose, a new dosing schedule, anew route of administration, a different duration of usage, a new age group (e.g., unique safety or effectiveness in the elderly), *another patient subgroup not explicitly identified in the current labeling,* a different stage of the disease, a different intended outcome (e.g., long-term survival benefit, improved quality of life, disease amelioration), effectiveness for a sign or symptom of the disease not in the current labeling; and *comparative claims to other agents for treatment of the same condition.*

63 Fed. Reg. at 31145 (emphasis added). Most of the cited examples of "new uses," if reasonably interpreted, are unobjectionable. However, patient subgroups and comparative claims are not examples of new uses; these references must be eliminated to make clear that the new dissemination provisions are not intended to apply to any practices that were permitted prior to enactment of Section 401.

For patient subgroups, as was the case prior to passage of Section 401, under the FFDCA a company can continue to distribute reprints proactively or otherwise include in its promotion statements describing *approved* uses of a drug in a particular patient population provided that the drug's approved indication contains no patient age limitation and the statements are adequately supported. See *generally 21* C.F.R. § 202.1(e)(6) & (7). Similarly, a company can continue to distribute reprints or include in its promotion statements concerning a study directly comparing one drug to another with respect to their approved indications even if the comparative claim is

not included in the product's labeling, so long as the comparison is adequately supported. See generally 21 C.F.R. § 202.1(e)(6)& (7). These practices under the FFDCA remain unaffected by Section 401. Accordingly, as the distribution of information regarding patient subgroups and comparative claims was permitted prior to the enactment of Section 401, it does not relate to a new use and does not fall within the elaborate procedures for the dissemination of new/unapproved uses. FDA must make this clear in its final rule by deleting the reference to patient subgroups and comparative claims and stating more generally that nothing in this regulation is intended to restrict practices involving promotion or the distribution of information that pre-existed the FDA Modernization Actor to subject otherwise permissible activities outside the scope of Section 401 to this new regulation.

2. Information That May Be Disseminated

a. "Scientifically Sound" Articles and Reference Publications [Proposed § 99.10 l(b)(l)]

FDA's proposed rule requires peer-reviewed journal articles and reference texts to contain a level of detail about reported clinical studies that could potentially exclude a number of high quality articles and most reference texts from dissemination. This is clearly not what Congress intended.

Section 401 provides that a company may disseminate reprints or copies of a peer-reviewed article "which is about a clinical investigation. . . and which would be considered to be scientifically sound by [qualified] experts." FFDCA § 552(a)(l)(B); 21 U.S.C. § 360aaa-l(a)(l)(B). Similarly, Section 401 authorizes dissemination of a reference publication "that includes information about a clinical investigation. . . that would be considered to be scientifically sound by experts qualified by scientific training or experience . . . ." FFDCA

§ 552(a)(1)(B); 21 U.S.C. § 360aaa-1(a)(1)(B). FDA's proposed rule deviates significantly from these statutory criteria.

Most significantly, FDA proposes to exclude peer-reviewed articles and reference publications that present a clinical investigation "in a format that does not represent a reasonably comprehensive presentation of the study design, conduct, data, analyses, and conclusions (e.g., letters to the editor, review abstracts, or abstracts of publications) . . . ." Proposed § 99.101(b)(l). Section 401 does not require that an article or reference publication describe clinical studies in a "reasonably comprehensive manner. " To the contrary, a peer-reviewed article need only "be about a clinical investigation," and a reference publication need only "include[] information about a clinical investigation," which experts would consider to be scientifically sound. The detail that FDA is requiring an article or reference publication to include resembles that which would be necessary for FDA's review of a supplemental product application. However, Section 401 is based upon the premise that the peer review process of nationally reputable medical and scientific journals and the publication process of widely distributed reference textbooks will ensure the scientific soundness of published material. FDA's statutorily limited review role prior to dissemination is focused on whether the material is objective and balanced. See FFDCA § 551(b)(6)(c); 21 U.S.C. § 360aaa(b)(6)(c). In clear contrast, FDA is authorized to conduct a full scientific review of the new use and the clinical studies supporting it when – as will occur in most cases – a supplement is filed.

The new requirements that FDA has proposed regarding the presentation of details about a clinical study could exclude many articles and reference publications of the very type Congress intended be disseminated. As to peer-reviewed articles, many summarize clinical trials in a manner that may potentially satisfy FDA's proposed criteria. At the same time, many quality

peer-reviewed articles may *not* present the level of detail that FDA appears to be contemplating, as FDA itself has previously recognized in other contexts. See FDA's Guidance on Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products at 17 (May 1998) ("[[S]tudy reports do not always contain a complete, or entirely accurate, representation of study plans, conduct and outcomes."). However, Congress clearly contemplated that virtually all peer-reviewed articles that have been accepted for publication in a nationally reputable journal of the type required by Section 401 would be considered scientifically sound, and such articles qualify for dissemination provided that the disseminated information is objective and balanced and that the other requirements of Section 401 are satisfied.

Moreover, review abstracts and abstracts of publications should not be precluded categorically from dissemination, as FDA has proposed. See Proposed § 99.101(b)(1). If a peer-reviewed abstract is about a scientifically sound clinical investigation, it satisfies the statutory criteria allowing for its dissemination even though it does not present comprehensive details about the clinical investigation.

As for reference texts, FDA states in the preamble to its proposed rule that "because reference publications rarely include detailed discussions of clinical investigations, FDA recognizes that the majority of such publications would probably not meet the requirements of section 401 of FDAMA and this proposed implementing regulation. " 63 Fed. Reg. at 31146. Any reading of Section 401 that would disqualify the majority of reference publications simply cannot be correct, because Congress provided for the dissemination of both journal articles *and* reference publications. Nothing in Section 401 indicates that reference publications stand on a lesser footing, or that Congress contemplated that companies could only disseminate such publications in limited circumstances. To the contrary, Congress established a more flexible

standard for reference publications, requiring only that they" *include []* information about a clinical investigation" (emphasis added). This statutory language differs from that for journal articles, which must "be about a clinical investigation," indicating that Congress understood that reference publications would contain less detailed reports of clinical trials and intended that a different and more flexible standard be applied to reference publications. FDA's proposed regulation violates the express terms of the statute by applying the same requirement for both reference publications and articles and by requiring that a reference publication present clinical studies in a detailed way not contemplated by Congress.

In order to eliminate the potential that high quality peer-reviewed articles in nationally reputable medical and scientific journals and widely distributed reference publications of the precise type Congress enacted Section 401 to cover will be disqualified under FDA's implementing regulations, FDA should delete its proposed Section 99.101 (b)(l) or revise it to remove any specific requirements for an article's or reference publication's presentation of clinical studies. Under the statute, it is sufficient for FDA to require simply that such materials be about, or include a discussion of, a clinical trial which qualified experts would consider to be scientifically sound.

b. "False or Misleading" Information [Proposed § 99.101(a)(4)]

In construing Section 40 1's requirement that disseminated information not be false or misleading, FFDCA § 552(a)(2); 21 U.S.C. 360aaa-1 (a)(2), FDA proposes that it

> may consider information disseminated under this part to be false or misleading if, among other things, the information includes only favorable publications or excludes articles, reference publications, or other information concerning risks and adverse effects that are or may be associated with the new use.

Proposed \ 99.101(a)(4). FDA's proposal contains several open-ended terms and concepts that, depending upon how they are construed and applied, could violate the statutory scheme by overly restricting the information that can be disseminated and creating unduly burdensome requirements for including additional information with a disseminated article or reference publication.

In particular, it is unclear what would constitute "other information about risks and adverse effects" that a company would have to include in a dissemination and what standard FDA would apply to determine whether such "other information" concerned risks and adverse effects that "may be associated with the new use. " Peer-reviewed articles in medical and scientific journals typically include information on adverse effects and safety. Such articles are objective and balanced as required by Section 401, and need not be accompanied by any other information. Moreover, the suggestion that any favorable publication must be accompanied by an unfavorable publication to avoid being misleading is arbitrary and exceeds the statutory requirements. While obvious concerns would arise from the dissemination of information about a positive study without disclosure of negative findings from other known studies, the touchstone of Section401 is objectivity and balance, and not all positive information need necessarily be accompanied by negative information.

Consistent with the statute, FDA should make clear that a single publication can be disseminated if it is objective and balanced and discusses appropriate safety information, regardless of whether its ultimate conclusions are stated favorably, neutrally, or negatively, FDA should also make clear that when additional materials must be included for balance, only scientifically sound data from clinical trials or peer-reviewed articles or reference publications

that are of the same caliber as those covered by Section 401 and that are about or include information about clinical trials, respectively, must be disseminated.

c. Accompanying Promotional Information [Proposed § 99.101(b)(2)]

In addition. to reiterating Section 40 1's requirement that disseminated articles and reference publications be unabridged, FDA's proposed rule would prohibit the dissemination of any information that is promotional in nature "with" an article or reference publication. Proposed § 99.101(b)(2). This proposal appears designed to maintain a clear separation between disseminated information and promotion. However, it is unclear what precisely would constitute the distribution of promotion "with" non-promotional disseminated materials.

FDA should clarify in its final rule that so long as promotional material concerns an approved use and is kept physically distinct from the disseminated information, FDA would not consider the two to be distributed together. For example, a company representative should be able to deliver an approved promotional piece on a labeled use and a qualifying article or reference publication on anew/unapproved use during the same visit to a physician's office. Provided the two sets of materials are physically distinct, there is no reasonable expectation that health care professionals could be misled, particularly given the mandatory disclaimers that must accompany the information on new uses. Any broader prohibition on the distribution of promotional material would be impractical given that company representatives will be calling on health care providers both before and after they provide information on new/unapproved uses in accordance with Section 401. Furthermore, no such constraints exist in Section 401, which provides simply that a disseminated article or reference publication be unabridged.

3. Mandatory Statements and Information

a. Disclosure That Use Has Not Been Approved **[Proposed §** 99.103(a)(l)]

Section 401 requires that a company include with disseminated information a "prominently displayed statement that discloses that the information concerns a use of a drug or device that has not been approved or cleared by the Food and Drug Administration." FFDCA § 55 l(b)(6)(A)(i); 21 U.S.C. § 360aaa(b)(6)(A)(i). FDA's proposed rule would extend this statutory requirement to mandate that a company utilize the precise statement "This information concerns a use that has not been approved by the FDA and is being disseminated under section 551 *et seq.* of the Federal Food, Drug, and Cosmetic Act." Proposed § 99.103(a)(l). Although it is helpful for FDA to provide a model disclosure statement that it considers appropriate, the Agency should not constrain companies to using a specifically worded disclosure. Any disclosure that is sufficiently clear and conspicuous satisfies the statutory requirement and should be acceptable under FDA's regulations. For example, companies should be able to state that the use of the drug has not currently been approved, or words to that effect, to explain in a factually accurate manner the drug's status.

The reference to "section551 et seq. of the Federal Food, Drug, and Cosmetic Act" is particularly unwarranted. Requiring a statutory reference serves no public health purpose and would likely confuse health care providers.

b. Placement of Mandatory Statements and Information [Proposed § 99.103(a)(l)(i)]

FDA's proposed rule, in addition to requiring a specifically worded disclosure statement, requires that a company "permanently affix the statement to the front of each reprint or copy of an article from a scientific or medical journal and to the front of each reference publication

disseminated under this part." Proposed § 99.103(a)(l)(i). If FDA requires that additional information be included with the materials that a company wishes to disseminate, such materials must also be attached to the front of the disseminated information. Proposed § 99.103(a)(4). These very detailed conditions exceed the requirements in Section401 and unnecessarily regulate a manufacturer's ability to disseminate information in a manner appropriate for a particular treatment and product. For example, FDA's proposal to require that mandatory information in addition to the disclosure regarding lack of FDA approval be attached to the front of disseminated information would be inappropriate in circumstances where it would be confusing for someone to read such information before even knowing what subject matter the disseminated information addressed. Section 401 requires only that the mandatory disclaimers be "prominently displayed," FFDCA § 551(b)(6)(A); 21 U.S.C. § 360aaa-1(b)(6)(A), and companies should retain a measure of discretion to meet this statutory requirement.

c." Additional Information Required by FDA [Proposed § 99.103(a)(4)& 99.301(3)]

In accordance with Section 401, FDA's proposed Section § 99.301(3) provides that FDA shall give a company notice and an opportunity for a meeting before requiring the company to include additional information or an objective statement prepared by FDA with the information that the company wishes to disseminate. FDA also references its authority to require that a manufacturer include additional information or an objective statement prepared by FDA in its proposed" Section 99. 103(a)(4); however, this reference does not specify that FDA will provide notice and an opportunity to meet before requiring the additional information. Section401 requires that FDA provide a company notice and an opportunity to meet before requiring it to include additional information with disseminated materials. FFDCA § 551(c); 21 U.S.C.

§ 360aaa(c). Accordingly, FDA should make clear that in all cases where additional information is being required, the Agency will provide a company notice and an opportunity to meet. Congress intended that FDA require the inclusion of such additional information only on a case by case basis, and notice and an opportunity to meet are critical to ensure that this intent is fulfilled.

4. Supplement Requirement

a. Economically Prohibitive Studies [Proposed § 99.205(b)(l)]

Section 401 provides that a company may receive an exemption from the requirement of submitting a supplemental application for the new use that is the subject of a dissemination if the company can show that "it would be economically prohibitive with respect to such drug or device for the manufacturer to incur the costs necessary for the submission of a supplemental application." FFDCA § 554(d)(2)(A); 21 U.S.C. § 360aaa-3(d)(2)(A). FDA proposes to limit this economic exemption to situations in which "the estimated cost of the studies needed for the approval of the new use would exceed the estimated total revenue from the drug or device less the cost of goods sold, and marketing, and administrative expenses attributable to the product .,. ." Proposed § 99.205(b)(l). This overly narrow approach directly contradicts the express provisions of Section 401 as well as Congress's intent, and will deny exemptions to products for which it makes no economic sense to pursue a supplement.

Section 401 makes clear that FDA's determination of whether it would be economically prohibitive to file a particular supplemental application must be based on a comparison of the costs and benefits associated with that supplement and the new use, not a comparison of the expected net revenues of the drug as a whole. Congress specifically provided that FDA "shall consider. . . the lack of the availability under law of any period during which the manufacturer

would have exclusive marketing rights *with respect to the new use involved."* FFDCA § 554(d)(2)(A)(i); 21 U.S.C. § 360aaa-3(d)(2)(A)(i) (emphasis added). Congress also required that FDA "shall consider. . . the size of the population expected to benefit *from approval of the supplemental application. "* FFDCA § 554(d)(2)(A); 21 U.S.C. § 360aaa-3(d)(2)(A) (emphasis added). FDA's proposed rule contradicts these statutorily-required considerations by changing the inquiry to the estimated net revenues from the drug as a whole. Nowhere has Congress stated that FDA should deny an application for exemption no matter how costly a supplement would be if a drug makes enough money from its other approved uses to compensate, as FDA has proposed.

In departing from the analysis that Congress has required, FDA's proposed approach would prevent companies from receiving an exemption for products for which it makes no economic sense to pursue a supplement. In effect, FDA's proposal would force companies to forgo use of Section401 under such circumstances notwithstanding the fact that Congress expressly created an exemption for economically prohibitive supplements. FDA should remedy this improper result by providing that a company will receive an exemption on economic grounds by showing that sales gained from approval of the supplement would not cover the costs of the supplement.

b. Submission of Applications for Exemptions Based on Economic Grounds [Proposed **§ 99.205(b)(1)(ii)]**

FDA's proposal would require companies seeking an exemption from the supplement requirement on the grounds that filing a supplement would be economically prohibitive to submit to FDA detailed sales and pricing information to justify the exemption. Proposed § 99.205 (b)(1)(ii). This approach raises serious concerns. First, FDA lacks the experience and

expertise to review sales and marketing projections. Second, although this information presumably would be exempt from release under the Freedom of Information Act, disclosing sales and pricing information to FDA implicates unusually significant confidentiality issues due to the proprietary and extremely sensitive nature of such information.

FDA should avoid these problems by providing that a report and certification of an independent auditor, accompanied by the attestation of a responsible company official, is sufficient to support an application for an exemption. In the preamble to its proposed rule, FDA specifically requested comment on requiring a report of an independent certified public accountant, made in accordance with the Statement on Standards for Attestation established by the American Institute of Certified Public Accountants, on the estimates submitted to support an exemption in lieu of or as an alternative to the attestation of a company official required by proposed Section 99.205 (b)(1)(ii)(C). Instead, FDA should require both a report from an independent certified public accountant and an attestation from a company official, and use the submissions as the documentary basis for the Agency's review of the application for exemption.

c. Extensions of Time for Completing Studies [Proposed § 99.303]

Section 401 provides that a company can meet the supplement requirement by certifying that it will conduct studies on the new use and file a supplement within 36 months. FFDCA § 554(c)(l); 21 U.S.C. § 360aaa-3(c)(1). FDA may extend the time for the completion of studies upon the request of a company for up to an additional 24 months. FFDCA § 554(c)(3)(B); 21 U.S.C. § 360aaa-3(c)(3)(B). FDA may also provide an extension upon its own determination that the studies cannot be completed and the supplemental application submitted within 36 months, FFDCA § 554(c)(3)(A); 21 U.S.C. § 360aaa-3(c)(3)(A). No limit is set upon the extension FDA may grant upon its own determination.

FDA's proposed rule essentially mirrors the statutory framework. *See* Proposed $99.303. Proposed Section 99.303(a), which deals with extensions made by FDA upon its own determination, does not include any limitation on extensions, unlike proposed Section 99.303(b), which references the two-year time limit for extensions made upon a company's request. FDA's proposed rule thus tracks Section 401. Nevertheless, FDA should make clear that Section 401 does not limit the extension time to two years in those cases where studies cannot be completed and submitted within 36 months or within 60 months. Such a situation could arise for certain trials (e.g., vaccine prevention trials or cancer trials) that can take longer than 5 years, and FDA has the discretion under Section 401 to grant longer extensions under those circumstances.

5. FDA Action on Submissions

a. Start of the 60-day Review Period [Proposed § 99.201]

Under Section 401, a company must submit to FDA the information it wishes to disseminate, along with other required information, 60 days before beginning dissemination. FFDCA § 551(b)(4); 21 U.S.C. § 360aaa(b)(4). FDA proposes to start this 60-day clock "when FDA receives a complete submission. . . ." Proposed § 99.201(d). FDA would consider a submission complete "if FDA determines that it is sufficiently complete to permit a substantive review." *Id.* FDA understandably has determined not to begin the 60-day review period until it receives a complete submission. However, nowhere in FDA's proposal would FDA notify a company that its submission has been received and determined to be complete. Companies would be left in the dark as to whether and when the 60-day clock started.

In order to avoid such confusion and the potential for delay, FDA should provide an official acknowledgement of the receipt of a submission and establish a set time period (e.g., 15 working days) within which it will notify a company whether its submission is complete, and if

not, what information is lacking. If a submission was complete as originally submitted, the 60-day clock would have started from the date of FDA's receipt of the submission. If a submission was not complete, a company would be able to submit additional information and FDA would again have a set time period within which to determine whether the application as supplemented is complete.

b. Protocols/Studies [Proposed § 99.301(b)(l)]

FDA's proposed rule provides that FDA shall review a company's proposed study protocols within the 60 days after receiving a submission and determine whether the protocols and proposed schedule are adequate. Proposed § 99.301(b)(l). FDA should further provide that if the Agency determines that the proposed protocols or schedule are not adequate, it will notify the company and provide an opportunity to meet. In particular, companies should be given an opportunity to discuss with FDA how much additional data, if any, are needed in addition to the information reported in the article or reference text to be disseminated. FDA should also clarify that a company can base its submission of planned studies under Section401 on ongoing clinical studies intended to support a supplemental application.

c. Notice and Opportunities to Meet Regarding Adverse Determinations [Various Proposed Provisions]

FDAs proposed rule expressly identifies only certain instances in which the Agency will provide notice and an opportunity to meet to a company concerning an adverse determination in connection with a proposed dissemination. See, e.g., Proposed § 99.301(a)(3)(i). FDA should make clear that it will provide notice and an opportunity to meet with a company concerning any adverse determination under these provisions. Adverse determinations concerning proposed

study protocols and schedules were already discussed above. In addition, FDA should provide notice and an opportunity to meet in at least the following situations:

- . FDA determines that a company does not comply with its requirements and cannot disseminate any information [Proposed § 99.301(a)(l)];
- . FDA requires a company to maintain records that will identify individual recipients of the information that is to be disseminated [Proposed § 99.301(a)(4)];
- . A company requests an extension of time for completing planned studies [Proposed § 99.303(b)];
- . FDA denies an application for exemption from the supplement requirement [Proposed § 99.305]; and
- . FDA terminates approval of an application of an exemption from the supplement requirement [Proposed § 99.403].

Providing for these additional opportunities to discuss adverse Agency determinations will expand the opportunities for dialogue between the FDA and regulated companies and facilitate the administration and application of this complex new mechanism for disseminating important new medical and scientific information to health care providers.

6. Corrective Action [Proposed § 99.401]

Under FDA's proposed rule, the Agency could order a company to cease disseminating information and to take corrective action if a supplemental application does not contain adequate information for approval of the new use. Proposed § 99.401(c)(1). However, in cases where a supplement establishing safety is not approved simply because it fails to establish effectiveness, FDA should not automatically require corrective action. Rather, corrective action should be reserved for situations in which some significant public health concern is identified that would be materially addressed by such corrective action,

FDA should also not order corrective action in a case where a company has certified that it will submit a supplemental application for the new use within six months and fails to meet that deadline, before meeting with the company to determine if there is good cause for the delay. *See* Proposed $$99.40 1(b)(2)(ii)&99.401 (c). Just as FDA provides that it will have an informal hearing in the case of a company that certifies it will conduct planned studies and submit a supplemental application within 36 months of dissemination before determining that a company has not acted with due diligence, FDA should meet with a company to determine if there is a good reason for the company's failure to meet the six month deadline before automatically requiring corrective action. For their part, companies should notify FDA as soon as possible regarding any deadlines that they think might not be met in order to permit a timely meeting with FDA about the situation.

At a minimum, companies should be given a clear mechanism for appealing any requirement that they take corrective action. Various avenues exist for making such appeals independent of Section401, including Section 404 of the FDA Modernization Act and21 C.F.R. $10.75. Nevertheless, for the sake of clarity, FDA should cross-reference those avenues in its regulations here.

7. Reporting Requirements [Proposed § 99.501]

Under FDA's proposed rule, companies must make semiannual reports to FDA following the initial dissemination of information on additional clinical research or other data relating to the safety or effectiveness of the new use and, if the company is conducting studies related to the submission of a supplemental application, periodic progress reports on the studies. Proposed § 99.501(b)(3)& (4). FDA should allow companies tosatisfy these obligations in accordance with standard IND/NDA reporting requirements. See, e.g.,21 C.F.R. $312.33 &21 C.F.R.

$314.81. The initial report could be accelerated or delayed to coincide with the established reporting date for the product, to be followed by reports every six months thereafter. These pre-existing reporting mechanisms will capture all of the information required by Section 401 and FDA's regulations, while streamlining the administrative compliance burdens.

FDA should also acknowledge at least in the preamble to its final rule that reports made under this section are exempt from disclosure pursuant to exemption 4 of the Freedom of Information Act and 21 C.F.R. § 314.430,

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The changes outlined above are necessary to bring FDA's proposed regulation in line with the text and spirit of Section401. As revised, FDA's regulations would facilitate the dissemination of valuable new medical and scientific information in the controlled manner authorized by Congress. Without such revisions, there is a grave risk that FDA's regulations will nullify, rather than implement, this important new statutory mechanism for providing health care providers with current treatment information.